Clinical Investigation

Clorazepate Use May Prevent Alcohol Withdrawal Convulsions

VICTOR G. HADDOX, MD, JD; T. GEORGE BIDDER, MD; LESTER E. WALDRON, *and* PATRICIA DERBY, *Sepulveda, and* SUSAN M. W. ACHEN, MPH, RN, *Van Nuys, California*

Clorazepate dipotassium was administered orally for the five-day prophylactic treatment of potential, incipient and overt withdrawal signs and symptoms in 226 patients on admission to an inpatient alcohol treatment unit. Conservative estimates based on these patients' histories and on literature reports predicted that between 7 and 40 (3% to 18%) of these persons would be expected to have a withdrawal convulsion. No patients experienced convulsions. This complete absence of seizures suggests that clorazepate is effective in counteracting convulsive and other manifestations of the alcohol withdrawal syndrome.

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The use of alcoholic beverages to the extent that physical dependence develops and withdrawal phenomena occur is a problem encountered in a relatively small percentage of persons who drink. Because of the extensive use of alcoholic beverages throughout the world, however, physicians frequently need to treat patients who are physically dependent on alcohol and who manifest withdrawal signs and symptoms or who have the potential for having these problems.

Physical dependence on alcohol is a major problem in those who seek help with alcohol misuse by enrolling in an alcohol treatment program. In the Sepulveda Veterans Administration Medical Center (VAMC) Alcohol Treatment Unit, a 35-day inpatient program, about two thirds of the 400 patients admitted annually to this facility show signs and symptoms of an alcohol withdrawal syndrome to the extent that medication to alleviate the symptoms is indicated.

In view of the prevalence of physical dependence on alcohol, it is essential to develop effective prophylactic methods for treating this problem that are safe and do not interfere with the physical, emotional and social rehabilitation that constitutes the major goals of alcohol treatment programs.

In this article we report a retrospective study of the use of the benzodiazepine, clorazepate, in 226 patients newly admitted to an inpatient alcoholism treatment unit who were either acutely intoxicated or experiencing an alcohol withdrawal syndrome. Clorazepate dipotassium was used prophylactically to treat potential, incipient and overt withdrawal symptoms. The anticonvulsant action of this agent, its long duration of action, its mild sedative effect, its high margin of safety and its cross-tolerance with alcohol have provided safe and effective therapy for patients who are frequently debilitated and who invariably have alcohol-related medical disorders.

The fact that no convulsive episode occurred in the 226 patients whose potential withdrawal syndrome was treated prophylactically with clorazepate is of clinical significance in view of a history of withdrawal convulsions in 18% of this group and literature estimates that grand mal convulsions occur in from 3% to 18% of alcoholic patients during withdrawal when no prophylaxis is given.

Methods

The Sepulveda VAMC Alcohol Treatment Unit is a 30-bed facility that provides an initial five-day detoxification period followed by a comprehensive 30-day program having the objectives of medical and psychological evaluation and treatment, rehabilitation, life-structuring and providing alternatives to drinking. During the 18-month period of the present retrospective study, 226 patients were detoxified with clorazepate. Of these patients, 41 (18%) had a well-documented history of at least one grand mal convulsion related to withdrawal from alcohol. A history of delirium tremens was present in 62 of these patients (27%), and virtually all had experienced withdrawal tremulousness in the past.

Each patient was detoxified with a regimen that included

- Magnesium sulfate, 2 grams given intramuscularly immediately upon admission, followed by 1 gram given intramuscularly every four hours for three doses;
- Clorazepate dipotassium, 15 mg given orally four times a day (day 1), three times a day (day 2), twice a day (day 3) and at bedtime (day 4); 7.5 mg at bedtime (day 5). In patients showing withdrawal signs and symptoms with this dose schedule, supplemental "as needed" oral doses of clorazepate, 15 mg every four to six hours, were available during the first three hospital days. About 25% of the patients required at least one supplemental dose.

This detoxification phase was followed by a 30-day rehabilitative period.

From the Alcohol Treatment Unit (Dr Haddox and Mr Waldron), the Department of Psychopharmacology (Dr Bidder), the Department of General Medicine (Mr Waldron) and the Research Service (Ms Derby), Veterans Administration Medical Center, Sepulveda; the Department of Psychiatry (Drs Haddox and Bidder), University of California, Los Angeles, School of Medicine, and the Valley Presbyterian Hospital Olmstead Memorial (Ms Achen), Van Nuys, California.

Reprint requests to Victor G. Haddox, MD, JD, Alcohol Treatment Unit, Veterans Administration Medical Center, 16111 Plummer St, Sepulveda, CA 91343.

ABBREVIATIONS USED IN TEXT

CNS = central nervous system
VAMC = Veterans Administration Medical Center

Results and Discussion

There was no occurrence of a grand mal convulsion in the 226 patients receiving the prophylactic clorazepate detoxification regimen.

The absence of seizure complications in this population of patients in the period immediately following the cessation of drinking is noteworthy for several reasons. First, these patients had a history of drinking heavily for several months before admission; 67% had clinically significant concentrations of alcohol—that is, more than 0.1 grams per dl—at the time of admission. Second is the expectation that seizures are likely to occur in from 3% to 18% of patients with severe alcoholism who stop drinking.[1,2] Third is the past history in 41 study patients (18%) of one or more recorded convulsive episodes during withdrawal from alcohol. The significance of this type of past history in predicting the likelihood of a convulsion occurring during withdrawal from alcohol is emphasized by the work of Tartara's group.[3] In a retrospective study these workers reported an incidence of convulsive manifestations in 10% of alcoholic patients during withdrawal. When they excluded cases with preexisting, potentially epileptogenic lesions, this percentage fell to 7%.

On the basis of these data, it can be anticipated that between 7 (3%) and 40 (18%) of the 226 study patients would have progressed to stage 3 in the alcohol withdrawal syndrome (see Table 1) and would have manifested withdrawal seizure activity if no prophylactic treatment had been instituted. It is of considerable significance that the symptoms in stage 2 among those patients were reduced, and more important, that no patient progressed to stage 3.

TABLE 1.—*Alcohol Withdrawal Syndrome**

Time of Appearance After Stopping or Significantly Reducing Alcohol Intake	*Symptoms*
Stage 1	
6 to 8 hours	Tremulousness, anxiety, startle reaction, autonomic hyperactivity (heart rate, blood pressure, diaphoresis, nausea, vomiting), hyperreflexia, craving for alcohol and other CNS depressants, sleep disturbance. Wernicke's encephalopathy and Korsakoff's disease present, but usually masked by more dramatic and acute symptoms
Stage 2	
24 hours	Hallucinations complicating persisting stage 1 phenomena, usually auditory or visual. May be other types and especially common at night when eyes are closed; need to differentiate from hallucinosis—an alcohol-related toxic psychosis
Stage 3	
7 to 48 hours	Grand mal convulsions that complicate persisting phenomena: generally multiple—2 to 6 in a 6- to 8-hour period, brief postictal period, probability of delirium tremens
Stage 4	
7 hours to 14 days	Global confusion complicating autonomic hyperactivity and hallucinations (delirium tremens), profound hyperthermia, hypertension, fluid electrolyte imbalance, vascular collapse, death

CNS=central nervous system

*Adapted and modified from Sellers and Kalant[4] and several other sources.

The development of tolerance and physical dependence to central nervous system (CNS) depressants such as alcohol is considered to be an adaptive or compensatory reaction that counters the depression of neuronal functions produced by these agents.[4] Discontinuance of, or an abrupt decrease in, alcohol ingestions leaves these stimulatory compensatory reactions unopposed, with a resulting increase in the neuronal excitability responsible for most of the signs and symptoms of the alcohol withdrawal syndrome. The grand mal convulsions that occur in the alcohol withdrawal syndrome are a striking manifestation of this hyperexcitability.

The well-established effects of the benzodiazepines in ameliorating signs and symptoms of the alcohol withdrawal syndrome involve several known pharmacologic actions of these compounds. These include the capacity for replacing the CNS depressant, alcohol, to which tolerance and physical dependence have been acquired. Of special relevance to the present study is these agents' anticonvulsant action[5] that is exerted on the propagation of the seizure process, rather than on the seizure focus, and that is considered to involve presynaptic γ-aminobutyrate-minergic mechanisms.[6]

Clorazepate has several pharmacologic attributes that make it a very useful agent for oral prophylactic treatment of the alcohol withdrawal syndrome. It has a long duration of action as a result of its in vivo conversion to desmethyldiazepam.[7] This avoids the risk that a withdrawal syndrome, such as frequently occurs with single doses of benzodiazepines that have a short half-life,[8] will intensify the alcohol withdrawal syndrome. The high margin of safety of clorazepate is reassuring when treating persons who have a high incidence of medical disorders. Finally, clorazepate lacks the euphorigenic, addiction-promoting action of certain benzodiazepines such as diazepam, chlordiazepoxide and alprazolam. This advantage, which is attested to by the unusual fact that no patient receiving clorazepate asked to have the drug therapy continued after the detoxification period was completed, is very important for its use in a group that has a predilection for drug dependency.

The occurrence of convulsions during alcohol withdrawal indicates a substantial degree of physical dependence and portends the possibility that delirium tremens can occur. Thus, clorazepate provides effective oral prophylactic therapy for this serious, unpredictable and potentially fatal complication of alcohol withdrawal. The safety and convenience of clorazepate make feasible its use in all patients requiring detoxification.

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